Estrogen Replacement Therapy and Endometrial Cancer Risk: Unresolved Issues

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Objective: **To clarify several unresolved issues regarding the relationship of estrogens to endometrial cancer risk.**

Methods: **We conducted a hospital-based case-control study involving 300 menopausal women newly diagnosed with epithelial endometrial cancer and 207 population controls matched to the cases for age, race, and residence.**

Results: **Estrogen use significantly increased endometrial cancer risk (adjusted relative risk [RR] 3.0, 95% confidence interval [CI] 1.7–5.1). Although both short- and long-term use appeared to elevate the risk of early-stage tumors, an effect of estrogens on late-stage tumors was observed only for long-term use (RR 2.1, 95% CI 0.7–6.4). A small proportion of women reported having used progestogens simultaneously with estrogens, which was associated with a lower risk (RR 1.8) than use of estrogens alone (RR 3.4). Although the highest risks were for recent users of estrogens, persistent excess risks were seen even for those who had discontinued use of 5 or more years. There were no striking relationships according to the type of estrogen or regimen used, and associations with dose were inconsistent, although women who used low-dose preparations exclusively had the lowest risk. Estrogen injections or creams, used by only 5.9 and 5.1% of the subjects, respectively, were not significant risk factors after adjustment for estrogen pill use. Women who were thin or who smoked cigarettes appeared to be most adversely affected by estrogen use. Estrogen users failed to experience the protective effect normally associated with oral contraceptive use.**

Conclusion: **The effect of estrogens on endometrial cancer risk appears to vary both by usage patterns and by patient characteristics.** ***(Obstet Gynecol 1993;81:265–71)***

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It is well established that endometrial cancer risk is greatly enhanced among long-term users of menopausal estrogens.[1–7] Despite many studies, relationships with specific patterns of use remain less well defined, including those involving dose, regimen, type of preparation, and mode of administration. In addition, controversy remains regarding duration of persistence of the excess risk associated with estrogen use. Further, although many studies have shown that estrogen use increases the risk of disease mainly within the uterine corpus (stage I), the extent to which estrogen use is associated with more advanced disease remains unclear.

Questions also persist regarding whether estrogen effects are altered by the presence of other endometrial cancer risk factors. A number of studies have shown that the associations with estrogen replacement therapy are strongest for thin women,[3,4,8–12] nondiabetics,[3,4] and normotensive women.[9,12] These findings suggest either that estrogen metabolism differs or that the risk is already sufficiently high in certain women that exposure to exogenous estrogens has a relatively small additional effect.

Most recently, questions have arisen regarding how the addition of progestogens affects the risk associated with estrogen therapy. Although combined estrogen-progestogen therapy for menopause has become increasingly common as a means of counteracting estrogen-induced endometrial hyperplasia,[13–17] the effects of combined hormone therapy on endometrial cancer have not been adequately addressed. We conducted a case-control study to clarify many of these unanswered questions.

Materials and Methods

This case-control study, described in detail elsewhere,[18] gathered cases from seven hospitals in five areas of the United States: Chicago, Illinois; Hershey,

Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina. Eligible women were newly diagnosed with endometrial cancer between June 1, 1987 and May 15, 1990, were between the ages of 20–74 years, resided in defined geographic catchment areas, and had not received previous treatment for their diseases.

For each eligible case, we attempted to select one control matched for age (same 5-year group), race, and residential area. For cases under the age of 65, we selected controls using random-digit dialing techniques,[19] with residence matched by telephone exchange. Older controls were derived from Health Care Financing Administration computer tapes, matching subjects to cases on zip code of residence. A short telephone questionnaire assessed whether subjects had undergone a hysterectomy; those not at risk of endometrial cancer were replaced with other eligible subjects.

Home interviews were conducted by uniformly trained interviewers. Interviews lasted a mean of 76 minutes and elicited detailed information on demographic factors, pregnancies, menstruation, contraceptive behavior, use of hormones, diet and alcohol intake, body size changes, smoking, medical conditions, and family history of cancer. For each episode of menopausal estrogen or progestogen pill use, answers were elicited on name of the preparation, date of first and last use, regimen of use, and actual use in days, weeks, months, or years during the exposure interval. If the respondent was taking estrogen and progestogen pills in the same month, she was questioned regarding the number of days each month that she took progestogens. Women were shown color photographs to assist their recall of specific preparations. Lists of preparations, categorized by alphabet, year first marketed, and color of preparation, were also used.

We obtained interviews from 434 of 498 eligible cases (87.1%) and from 313 of 477 eligible controls (65.6%). The main reason for non-response was refusal (4.8% of cases and 21.8% of controls). The response rate was considerably higher for the random-digit dialing than for the Health Care Financing Administration controls (76.3 versus 46.8%), primarily because of a lower refusal rate among the younger women (16.8 versus 30.6%).

Odds ratios, as estimators of relative risks (RRs), were calculated to assess the effect of hormone use on endometrial cancer risk. Because of the large number of subjects without an interviewed matched subject, we chose unconditional logistic regression as the means of deriving maximum likelihood estimates of RRs and 95% confidence intervals (CIs).[20] Tests for trend were obtained by categorizing the exposure variables and treating the scored variables as continuous, after eliminating unknown values. Multiplicative terms were used to test the statistical significance of interactions.

The present analysis was limited to cases of epithelial cancer and to women who were naturally menopausal (300 cases and 207 controls). The majority of the subjects were from Illinois (N = 78), California (N = 70), or Pennsylvania (N = 63), with fewer deriving from North Carolina (N = 46) or Minnesota (N = 43). For select analyses, we subdivided cases into early versus late stage at diagnosis. A total of 222 tumors (74.0%) were restricted to the uterine corpus, whereas 75 (25%) involved spread outside of the uterus or extension into the endocervical canal; three (1.0%) were unclassifiable.

Results

The mean age of the cases at interview was 63.3 years, compared to 63.0 years among the controls. Cases and controls were comparable for race, with the majority classifying themselves as non-Hispanic whites. Cases had significantly more education, fewer births, higher weights, earlier ages at menarche, less oral contraceptive (OC) use, more frequent histories of diabetes, and less common cigarette smoking histories than controls (Table 1). Unlike other investigators, we failed to find a significant effect of late age at natural menopause on endometrial cancer risk. Estrogen users tended to have fewer births, lower weights, more common smoking histories, and more frequent use of OCs than nonusers of estrogens. Thus, we considered these factors, along with the matching factor of age, as potential confounders to the estrogen associations and included them in all regression models. Adjustment for additional variables, including study site, had no appreciable effect on the derived risk estimates.

A total of 24.0% of the cases versus 14.0% of the controls reported having used estrogens, resulting in an adjusted RR of 3.0 (95% CI 1.75–5.1) (Table 2). Risk increased significantly ($P < .001$) with years of use of estrogens, with users of 5 or more years having a sixfold excess risk. Users for 10 or more years had an even further increased risk (RR 16.1, 95% CI 5.1–50.5). Risk also increased with increasing interval since first use of estrogens, but this effect appeared to be explained by the tendency of those with long intervals since first use to be long-term users of estrogens. The highest risks were observed for recent users (less than 5 years since last use) (RR 4.0, 95% CI 2.0–8.0). However, we noted a nonsignificant excess risk even

Table 1. Distribution of Endometrial Cancer Cases and Controls by Selected Risk Factors

	Controls (N = 207)	Cases (N = 300)	RR*	95% CI
Education (y)				
<12	31.4%	23.7%	1.0	
12	31.9%	31.0%	1.4	0.8–2.3
13–15	18.8%	15.0%	1.6	0.8–3.0
≥16	16.9%	28.7%	2.8	1.5–5.0
No. of births				
0	9.7%	19.0%	1.0	
1–2	33.8%	37.0%	0.6	0.3–1.1
≥3	56.5%	44.0%	0.4	0.2–0.8
Body mass index (kg/m^2)				
<24	37.2%	28.0%	1.0	
24–27	34.3%	19.0%	0.7	0.4–1.2
≥28	26.6%	52.0%	2.7	1.6–4.4
Age at menarche (y)				
≥14	34.3%	23.7%	1.0	
13	29.5%	26.0%	1.1	0.6–1.8
<13	35.3%	50.0%	1.8	1.1–2.9
Years of use of combined OCs				
None	75.4%	88.7%	1.0	
<5	13.0%	6.7%	0.5	0.2–0.9
≥5	10.6%	3.7%	0.3	0.1–0.7
History of diabetes				
No	91.3%	83.7%	1.0	
Yes	8.7%	15.0%	1.8	0.9–3.4
Cigarette smoking				
No	57.5%	70.3%	1.0	
Yes	42.5%	28.3%	0.5	0.4–0.8

RR = relative risk; CI = confidence interval; OCs = oral contraceptives.

* Relative risks are adjusted for age plus all risk factors shown. Missing values were included in the analyses, but are not shown in the table.

among those who had discontinued use 5 or more years before diagnosis (RR 1.9). No distinctive trends arose according to age at first use, although women whose use began at age 55 or later were not at excess risk because of unusually short exposure.

When we examined the effects of estrogen use according to stage of disease at diagnosis, we saw a significant relationship for the early-stage tumors (RR 4.1, 95% CI 2.3–7.5), with the risk being particularly elevated for women with 5 or more years of use (RR 8.6, 95% CI 3.7–20.0). Estrogen use was not a risk factor for late-stage tumors when short-term use was involved, but users for 5 or more years experienced a nonsignificant elevation in risk (RR 2.1, 95% CI 0.7–6.4).

Four percent of the women reported simultaneous use of estrogens and progestogens, with such use being associated with a nonsignificant and lower risk (RR 1.8) than use of estrogens alone (RR 3.4, 95% CI 1.8–6.3). Risk did not vary substantially by the number of days per month that progestogens were used or by the duration of progestogen use. Although users of estrogens combined with progestogens had a lower risk of early-stage tumors than did users of estrogens alone, it was noteworthy that combined exposure was still associated with a nonsignificant elevation in risk (RR 2.4).

To explore more fully the persistence of the excess risk associated with estrogen use, we examined risk according to a cross-classification of years of use and years since last use of estrogens (Table 3). Among long-term, recent users (ie, those with 5 or more years' use and less than 5 years since last use), a particularly high risk was noted (RR 9.9, 95% CI 3.5–28.0). However, a nonsignificant excess risk (RR 2.4) persisted even among long-term users who had discontinued use in the more distant past. Among short-term users, risks were similar for recent and non-recent users.

Table 2. Relative Risks of Endometrial Cancer by Estrogen Use and Stage of Disease at Diagnosis

	Control	All cases			Early-stage cases			Late-stage cases		
	(N)	N	RR*	95% CI	N	RR*	95% CI	N	RR*	95% CI
Estrogen use										
No	176	222	1.0†		158	1.0†		62	1.0†	
Yes	29	72	3.0	1.7–5.1	62	4.1	2.3–7.5	9	1.0	0.4–2.4
Years estrogens used										
<5	19	25	1.4	0.7–2.9	22	1.9	0.9–4.2	3	0.5	0.1–1.8
≥5	10	47	6.0	2.7–13.1	40	8.6	3.7–20.0	6	2.1	0.7–6.4
Years since last use										
<5	16	48	4.0	2.0–8.0	41	6.7	3.0–14.8	6	1.2	0.4–3.5
≥5	13	24	1.9	0.9–4.2	21	2.3	1.0–5.2	3	0.7	0.2–2.9
Combined estrogen-progestogen use‡										
No (estrogens alone)	19	60	3.4	1.8–6.3	52	4.7	2.4–8.9	7	1.2	0.5–3.2
Yes	9	11	1.8	0.6–4.9	9	2.4	0.8–7.8	2	0.6	0.1–3.3

Abbreviations as in Table 1.

* Relative risks are adjusted for age, number of births, body mass index, smoking, and years of use of oral contraceptives. All risks are relative to non-users of estrogens. Missing values were included in the analyses, but are not shown in the table.

† Referent group for all risks.

‡ Defined as women who had used both estrogens and progestogens for 3 or more months.

Table 3. Relative Risks of Endometrial Cancer by Years of Use and Years Since Last Use of Menopausal Estrogens

Years of use	Years since last use	
	<5	≥5
<5		
RR*	1.2 (11, 11)†	1.7 (8, 14)
95% CI	0.4–3.2	0.6–4.6
≥5		
RR*	9.9 (5, 37)	2.4 (5, 10)
95% CI	3.5–28.0	0.7–7.9

Abbreviations as in Table 1.

* Relative risks are adjusted for age, number of births, body mass index, smoking, and years of use of oral contraceptives. All risks are relative to non-users of estrogens (176 controls, 222 cases).

† Numbers of controls, cases are shown in parentheses.

We further assessed the risk of endometrial cancer according to type, dose, and regimen of estrogen use (Table 4). The risk associated with the exclusive use of conjugated estrogens (RR 2.9, 95% CI 1.6–5.3) was similar to that for nonconjugated estrogens (RR 2.4), although the latter was not statistically significant. When the dose of the conjugated estrogen used longest was considered, no distinctive patterns were apparent. However, an analysis of the risk according to exclusive use of low-dose preparations (less than 1.25 mg) revealed a lower and nonsignificant excess risk (RR 1.9) for this exposure pattern than when use included higher doses (RR 3.3, 95% CI 1.5–7.3). This effect appeared to be independent of years of use, with long-term (5 years or longer) users of high-dose pills having an RR of 3.9 and long-term users of exclusively low-dose pills having an RR of 7.3. The majority of the women reported cyclic use of estrogens (eg, 3 weeks on, 1 week off), associated with an RR of 2.9 (95% CI 1.4–5.7), whereas daily use resulted in an RR of 2.5 (95% CI 1.1–5.8).

A total of 5.9% of the women reported having had injections of estrogens, and 5.1% reported having used vaginal creams. These exposures appeared initially to be associated with elevated risks, but after adjustment for estrogen pill use and other risk factors, neither injections (RR 1.3) nor creams (RR 1.5) were significantly related to risk.

When the effects of estrogen use were compared across varying levels of other risk factors (calculating the ratio of RRs between users and non-users), there was no indication that parity status influenced the effects; however, thin women and smokers appeared to be more adversely affected (Table 5). Although the interaction of estrogen use with body mass was statistically significant ($P = .03$), that with cigarette smoking was not ($P = .18$). Estrogen use was associated with similar effects in users and non-users of OCs, but users of estrogens did not experience the protective effects normally associated with the use of OCs (RR 1.2 compared with non-users of either preparation).

When estrogen effects were examined according to histories of selected diseases, there was some evidence that women with a history of benign breast disease and those with self-diagnosed problems with hirsutism were more adversely affected by estrogen use than women without either of these conditions. However, neither of these interactions was statistically significant (respective P values of .25 and .14). There was no evidence of an interactive effect between estrogen use and a history of several other conditions, including diabetes, hypertension, thyroid diseases, endometriosis, or self-diagnosed problems with facial acne, although several of these analyses were limited by small numbers.

Discussion

Although this epidemiologic study focused on a hospitalized series of patients, who were more willing to participate than matched population controls, the data collected were unique in allowing a number of evaluations, including the interactive effects of hormones with other endometrial cancer risk factors and relationships for late-stage tumors. Estrogen use was associated with a significant threefold elevation in the risk of

Table 4. Relative Risks of Endometrial Cancer by Type, Dosage, and Regimen of Estrogen Use

	Controls	Cases	RR*	95% CI
Type of estrogen used				
Only conjugated	21	58	2.9	1.6–5.3
Only nonconjugated or combination of both types	7	13	2.4	0.8–6.6
Dose of estrogen used longest†				
0.3 mg	2	4	2.8	0.4–19.3
0.625 mg	9	26	4.0	1.6–9.9
≥1.25 mg	5	15	2.8	0.9–8.6
Unknown	1	6		
Exclusive use of low-dose pills				
Yes	16	30	1.9	0.9–3.8
No	11	31	3.3	1.5–7.3
Unknown	1	10		
Usual regimen of use				
Every day	10	20	2.5	1.1–5.8
Cyclically	16	41	2.9	1.4–5.7
Other	2	6	4.6	0.8–26.0
Unknown	0	4		

Abbreviations as in Table 1.

* Relative risks are adjusted for age, number of births, body mass index, smoking, and years of use of oral contraceptives. All risks are relative to non-users of estrogens (176 controls, 222 cases).

† Restricted to conjugated estrogens without added methyltestosterone.

Table 5. Relative Risks of Endometrial Cancer Among Menopausal Women by Combined Effects of Estrogen Use and Other Risk Factors

	Non-users of estrogens			Estrogen users			Ratio of RRs of users/ non-users†
	No. controls, cases	RR*	95% CI	No. controls, cases	RR*	95% CI	
No. of births							
0	16, 34	1.0‡		4, 21	3.2	0.9–11.3	3.2
≥1	160, 188	0.5	0.3–1.1	25, 51	1.7	0.7–3.9	3.1
Body mass index (kg/m^2)							
<28	126, 87	1.0‡		22, 50	3.8	2.0–7.2	3.8
≥28	46, 133	4.3	2.7–6.8	7, 22	4.5	1.8–11.4	1.0
Cigarette smoker							
No	101, 164	1.0‡		17, 44	2.3	1.2–4.4	2.3
Yes	75, 55	0.5	0.3–0.8	12, 28	2.4	1.1–5.5	4.7
OC use							
Non-user	137, 198	1.0‡		19, 62	2.8	1.5–5.0	2.8
User	39, 24	0.5	0.3–0.9	10, 10	1.2	0.4–3.1	2.4
Benign breast disease							
No	142, 189	1.0‡		25, 60	2.6	1.4–4.7	2.6
Yes	34, 30	0.8	0.5–1.5	4, 12	4.8	1.4–16.7	5.8
Hirsutism							
No	162, 176	1.0‡		28, 60	2.7	1.4–4.4	2.7
Yes	14, 43	1.8	0.9–3.6	1, 12	21.5	2.4–195	11.8

Abbreviations as in Table 1.

* Relative risks are adjusted for age, and, when appropriate, for number of births, body mass index, smoking, and years of use of oral contraceptives. Missing values were included in the analyses, but are not shown in the table.

† Calculation of ratios used relative risks with more precision than those shown.

‡ Referent group for subgroup analysis.

endometrial cancer. As in a number of other investigations,[1,2,4,6,7,11,12,21,22] the risk associated with estrogen use was particularly high for early-stage tumors. Thus, for these tumors, long-term use was associated with an 8.6-fold excess risk, but even use of less than 5 years resulted in approximately a doubling of risk. Although the numbers of subjects with late-stage tumors were more limited, it was noteworthy that long-term users still had a nonsignificant twofold excess risk of these cancers, an effect noted in several other studies.[6,22,23]

An unresolved issue with respect to menopausal estrogens is how long the excess risk associated with their use persists after discontinuation. Although one investigation showed a fairly precipitous decline in risk after cessation of use,[9] most studies have found that the excess risk associated with estrogen use persists for at least 5 years after discontinuation.[5–7,23] Similarly, we found that the excess risk can persist for at least 5 years after discontinuation, particularly when preceded by long-term exposure.

Relationships of endometrial cancer risk with estrogen dose, regimen, type of preparation, and mode of administration are also of interest. Although several previous studies have found elevated risks associated with higher doses of estrogens,[1,2,7,11,21] we failed to observe a dose-response relationship for the estrogen used longest. This may reflect the difficulty in assessing dose relationships among women who have taken multiple types of pills; thus it is noteworthy that women who reported exclusively using lower-dose (less than 1.25 mg) preparations had less risk than those using higher-dose preparations. However, exclusive users of low-dose pills remained at a nonsignificant excess risk, failing to support the findings of Rubin et al[23] that this is not a hazardous exposure. With respect to regimen of use, we found no higher risk associated with daily as opposed to cyclic use, in contradiction to the findings by some[11,21] but in agreement with others.[1,7,9] As in a number of investigations,[1,2,7,11] we found endometrial cancer risks to be elevated for both nonconjugated and conjugated estrogens, contradicting findings that nonconjugated estrogens are unrelated to endometrial cancer risk.[9,24] Finally, we attempted to evaluate whether routes of administration other than oral were associated with elevated endometrial cancer risk. Although we initially found high risks associated with both injections and vaginal creams, these appeared to be confounded by oral use of estrogen pills. Thus, after adjustment, estrogens in forms other than pills were no longer significant risk factors, in accord with results from another investigation.[2]

Although there is now little doubt that unopposed

estrogen use increases the risk of endometrial cancer, it remains unclear whether the excess risk can be eliminated by the addition of a progestogen. The favorable effects of progestogens on the endometrium are well recognized, but they have not been adequately quantified with respect to endometrial cancer risk. One Swedish investigation noted a 40% excess risk associated with estrogen therapy alone, which was completely eliminated by the addition of a progestogen for the entire treatment period.[25] However, the women in that study were primarily exposed to estradiol, a preparation not commonly used in the United States. Of more relevance to American women is a recent investigation by Voight et al,[26] in which unopposed estrogen use was associated with an RR of 5.7, which decreased to 1.6 when a progestogen was used for at least 6 months. Although in our study, use of estrogens alone was associated with a somewhat lower risk (RR 3.4), the risk associated with combined therapy was nonsignificant and quite similar to that observed by Voight et al (RR 1.8). In the former study, the risk was lower when progestogens were used for 10 or more days as compared with fewer days of the month; this effect was not seen in our study although small numbers were involved. However, we did find that combined therapy continued to result in a nonsignificant excess risk of early-stage tumors (RR 2.4), although of lower magnitude than when estrogens were used alone (RR 4.7). Even though both our study and that of Voight et al included few numbers of women exposed to combination therapy, it appears that this mode of administration has definite beneficial effects on cancer risk. However, further epidemiologic studies are needed to clarify the optimal regimen of use for assuring no residual adverse effects of estrogens.

Of particular interest in this study was the evaluation of estrogen effects according to the presence of other endometrial cancer risk factors. Although several investigators have noted stronger effects of estrogens in women of low parity,[27] thin women,[3,4,8–12] normotensive women,[9,12] and non-diabetics,[3,4] these interactions have not been consistent. We failed to support the notion of a more adverse effect of estrogens among nulliparous women, normotensive women, or non-diabetics, although the latter interaction, in particular, was limited by small numbers of women. We did find support for an enhanced effect of estrogens among thin women. This finding is consistent with the observation that obese women may be less susceptible to the effects of exogenous hormones because of enhanced conversion of androstenedione to estrone in adipose tissue, lower levels of sex hormone-binding globulin, and greater bioavailability of estrogens.[28]

Cigarette smoking has recently been noted in a number of investigations to be associated with strong reductions in endometrial cancer risk,[29] an effect also observed in our study, although only among non-users of estrogens. The biologic mechanism for the effect is still unknown, although smoking has been noted to affect the absorption, distribution, and metabolism of hormones. Thus, it is noteworthy that we found a stronger effect of exogenous estrogens among smokers, as noted elsewhere.[23] Our findings may imply a common mechanistic pathway for smoking and estrogen use on the risk of endometrial cancer, an issue that merits future attention. Also deserving of further attention is the interaction that we detected between estrogen use and problems with hirsutism, particularly given evidence that endogenous hormonal alterations can predispose to the condition.[30]

Given that women are being increasingly exposed to both OCs and menopausal estrogens, it is of interest to evaluate the joint effects of these two preparations, especially because they appear to have very different effects on endometrial cancer risk. In this study as well as in others,[31–34] OCs were found to be associated with substantial reductions in risk. Rubin et al[23] found that women who had used both preparations had no increased risk relative to non-users, and suggested that OCs may render the endometrium less susceptible to the effects of exogenous estrogens. However, we found that estrogen use was associated with a similar excess risk in both users and non-users of OCs. Thus, although women exposed to both agents were not at excess risk relative to non-users, these women did not experience the apparent beneficial effect of previous use of OCs.

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